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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/637,190	08/11/2000	Mien-chie Hung	12005-002001	8780

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/637,190	HUNG ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-20 are pending and under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. The rejection of claims 1-20 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record.

Claims 1, 2, 4, 6, 7, 9, 11, 12, 14, 16, 17 and 19 are vague and indefinite in the recitation of "threshold level". The term "threshold level" in claims 1, 6, 11 and 16 is a relative term which renders the claims indefinite. The term "threshold level" is not defined by the claims, the specification does not provide a definition of "threshold level" wherein one of ordinary skill in the art would be reasonably apprised of the scope of the invention. The specification describes methods by which the "threshold level" can be empirically determined on page 2, lines 3-10. However, this does not constitute a limitation whereby the metes and bounds of the claims can be determined. Furthermore, It is noted that the specification states "The threshold levels of expression for exclusion or inclusion in any group is set to achieve pre-determined levels of survival". Thus, a pre-determined survival probability must be known in order to segregate patients on the basis of Maspin expression. As the claims 1-10 are drawn to determining a probability of survival, it appears that the guidance given in the specification is not adequate for the determination of a "threshold level".

Applicant argues that the examiner is misinterpreting "pre-determined levels of survival" with "probability of survival" and that pre-determined levels of survival are established based on the actual survival curves of patients according to the method disclosed in the instant specification. Applicant argues that because the specification clearly describes a method of obtaining the former and determining threshold levels, the claims at issue are definite. This has been considered but not found persuasive. It is noted that the claims were not rejected for lack of enablement, but for failing to conform to the standards set by 112, second paragraph. Applicants

arguments regarding the actual survival curve of patients according to the method set forth are not persuasive because the claims do not incorporate the survival curve of said patients, thus applicants are arguing limitations which are not part of the claims. Further, it is obvious that the pre-determined level of survival can be fixed to almost any value based on the pre-determined survival probability. Thus, the threshold value is vague and indefinite because it is an object which is variable.

4. The rejection of claims 1-20 under 35 U.S.C. 103(a) as being unpatentable over Sager et al (USP 5,470,970) in view of the abstracts of Ding et al (Proc Amer Assoc Cancer Res, 1996, Vol. 37, page 90) , and Rheinwald et al (Cancer Research, 1981, Vol. 41, pp. 1657-1663) and Pemberton et al (J. Of Histochemistry & Cytochemistry, 1997, Vol. 45, pp. 1697-1706) and the abstracts of Petrovich et al (Radiology, 1982, Vol. 144, pp. 905-908) and Weber et al (Otolaryngology-Head and Neck Surgery, 1988, Vol. 99, pp. 16-23) and Tytor et al (Clinical Otolaryngology, 1990, Vol. 15, pp. 235-252) and Eiband et al (American Journal of Surgery, 1989, Vol. 158, pp. 314-317) and Huwer et al (European Journal of Cardio-Thoracic Surgery, 1992, Vol. 6, pp. 498-502) and Nagel et al (Zentralblatt fur Chirurgie, 1994, Vol. 119, pp. 225-232) and van der Velden et al (Cancer, 1995, Vol. 75, pp. 2885-2890) is maintained for reasons of record.

Claim 1 is drawn to a method of determining the probability of survival for a subject with squamous cell carcinoma, the method comprising determining the level of Maspin gene expression in a biological sample and comparing said level with a threshold level, wherein a level of gene expression in the biological sample which is above the threshold level is indicative of a relatively high probability of survival. Claim 6 is drawn to a method of determining the probability of survival for a subject with squamous cell carcinoma, the method comprising determining the level of Maspin gene expression in a biological sample and comparing said level with a threshold level, wherein a level of gene expression in the biological sample which is below the threshold level is indicative of a relatively low probability of survival. Claim 11 is drawn to a method of determining whether a subject with squamous cell carcinoma does not have a lymph node containing cancerous cells, the method comprising determining a level of Maspin gene expression in a biological sample and comparing the level with a threshold level,

wherein a level of Maspin gene expression above the threshold level is indicative that the subject does not have a lymph node containing cancerous cells. Claim 16 is drawn to a method of determining whether a subject with squamous cell carcinoma does not have a lymph node containing cancerous cells, the method comprising determining a level of Maspin gene expression in a biological sample and comparing the level with a threshold level, wherein a level of Maspin gene expression below the threshold level is indicative that the subject has a lymph node containing cancerous cells. Claims 2, 7, 12 and 17 embody the methods of claims 1, 6, 11 and 16 respectively, wherein Maspin gene expression is determined by measuring Maspin protein. Claims 3, 8, 13 and 18 embody the methods of claims 2, 7, 12 and 17 respectively, wherein the amount of Maspin protein is determined by an antibody that specifically binds to Maspin. Claims 4, 9, 14 and 19 embody the methods of claims 1, 6, 11 and 16, respectively, wherein Maspin gene expression is determined by measuring Maspin mRNA. Claims 5, 10, 15 and 20 embody the methods of claims 4, 9, 14 and 19, respectively, wherein the level of Maspin mRNA is determined by Northern Blot.

Sager et al teach a method for staging a carcinoma wherein the carcinoma is derived from cells which normally express the Maspin gene, said method comprising the detection of Maspin gene mRNA by northern blot. Sager et al teach that wherein the amount of hybridization complex detected is less than about one-half, more preferably less than about one-third, and more preferably less than about one-tenth the amount found in the non-cancerous control cell, the quantity of said hybridization complex is indicative that the test cell is cancerous, whereas the absence of a hybridization complex with the mRNA of the test cell is indicative that the test cell is from an advanced, probably metastatic carcinoma. Sager et al teach determination of the hybridization complex by Northern Blot (column 4, lines 24-57). Sager et al also teach the detection of the Maspin protein by means of monoclonal or polyclonal antibodies, and the same correlation between the relative level of the immunocomplex in the test sample to the control sample (column 4, line 58 to column 5, line 15). Thus, Sager et al teaches the correlation between Maspin gene expression in carcinomas and the relative likelihood of metastasis. Sager et al does not specifically teach squamous cell carcinoma as a type of carcinoma, but teaches that the suspected carcinoma is derived from a type of cell which normal expresses the Maspin gene to a significant and easily detectable degree (column 4, lines 21-26).

The abstract of Ding et al teaches that the squamous cell carcinoma line of SCC4 highly expresses the Maspin protein. The abstract further teaches that Maspin plays a role in several human tumors including those of the tongue and endometrium and that Maspin was commonly overexpressed in squamous cell carcinomas.

Rheinwald et al teach that the SSC4 cell line was derived from human squamous cell carcinoma of the tongue (page 1658, first column, lines 2-3).

Pemberton et al teach that Maspin is highly expressed in the endometrium of the uterus and the squamous epithelium of the tonsil (page 1701, second column, lines 6-15 under the heading "Discussion").

The abstract of Petrovich et al and Weber et al and Tytor et al and Eiband et al and Huwer et al and Nagel et al and van der Velden et al all teach the correlation between metastasis to lymph nodes and poor survival in patients having squamous cell carcinoma.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to correlate the absence of a hybridization complex or an immunocomplex with metastasis to the lymph nodes and poor probability of survival in patients having squamous cell carcinomas of the tongue, uterine endometrium or tonsil; it would also have been obvious to correlate the decrease of Maspin gene expression with an early stage carcinoma that is probably not metastatic with relatively high probability of survival and a low probability of lymph node metastases in patients having squamous cell carcinomas of the tongue, uterine endometrium or tonsil. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Sager et al on the correlation between Maspin gene expression and the likelihood of metastasis in carcinomas derived from a cell type which normally expresses Maspin, the teachings of the abstract of Ding et al on the common over expression of Maspin in squamous cell carcinomas and the role of Maspin expression in human tumors of the tongue and endometrium, the teachings of Pemberton et al on the expression of Maspin in normal tissues of the uterine endometrium and the tonsil. One of skill in the art would have recognized that squamous cell carcinomas of the tongue, uterine endometrium and tonsil are carcinomas derived from a type of cell which normally expresses the Maspin gene, and thus the correlations of Maspin expression and metastatic cancer as taught by Sager et al apply to squamous cell carcinomas of the tongue, uterine endometrium and tonsil.

Further one of skill in the art would recognize that the presence of lymph node metastases would be prognostic for poor survival in patients with squamous cell carcinoma according to the teachings of Petrovich et al and Weber et al and Tytor et al and Eiband et al and Huwer et al and Nagel et al and van der Velden et al.

Applicant argues that the teachings of Sager are based on the observation that the level of Maspin expression decreases during progression to breast cancer, and that there is no indication in Sager et al that the level of Maspin expression also decreases during progression to squamous cell carcinoma . Applicant maintains that Ding et al teach away from the instant invention because Ding et al teaches that Maspin was commonly overexpressed in squamous cell carcinoma cell lines. This has been considered but not found persuasive.

Sager teaches the breast cancer progression and the decrease in Maspin level as a specific embodiment. Sager et al provide general teachings regarding the decrease in Maspin levels and the cancerous state and the absence of Maspin transcription levels and the state of metastatic carcinoma. Sager et al teach that the determination of whether or not a cell or tissue is cancerous or metastatic based on decreasing or absent levels of Maspin gene expression can be applied to any cell which normally expressed the Maspin gene product to a significant and easily detectable degree. Pemberton et al identify the uterine endometrium and the squamous epithelial of the tonsil as normal tissues ion which the Maspin gene product is highly expressed. Regarding the expression of Maspin in the SCC4 ell line, it is noted that Ding et al teach that the level of the Maspin gene product is highly expressed. Ding et al do not teach that the level of the Maspin is overexpressed in the primary tumor which is metastatic. Further, one of skill in the art recognizes that a cell line undergoes alterations in gene expression when adapting to culture conditions. One of skill in the art would not expect that the relative level of gene products in a cell line would strictly parallel the level of gene product in a tumor in situ ding et al is relied upon in the instant rejection as an indication that squamous cell carcinoma of the tongue would be a type of cell which normally expresses the Maspin gene to a significant and easily detectable degree, as the Maspin gene product was easily detectable in the SSC4 cell line. Additionally, one of skill in the art would recognize that squamous cell carcinomas originating from the squamous epithelial of the uterus and tonsil would also be expected to have a decreased or absent level of Maspin gene product in carcinomas which have become metastatic. One of skill in the

art would recognize that the normal uterine endometrium and the normal tonsil had levels of Maspin which were easily detectable and therefore the teachings of Sager et al regarding the decreased levels f Maspin gene product relative to the progression of cancer and metastatic cancer would apply.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
December 21, 2003